REMARKS

Claims 18-26 are pending. Claims 1-17 have been cancelled and new Claims 18-26 drafted for ease of examination. Support for new Claims 18-26 derives from the specification and claims as originally filed. Accordingly, the new claims do not present new matter and entry is proper.

Rejections under 35 USC § 112, second paragraph

Claims 13 and 14 are rejected under 35 USC § 112, second paragraph as being indefinite. Claims 13 and 14 have been cancelled; thus the rejection is moot. Applicants respectfully request withdrawal of the rejection.

Rejections under 35 USC § 112, first paragraph

Claims 1, 2, 5-7, 10-14, 16 and 17 are rejected under 35 USC § 112, first paragraph for lack of enablement. In particular, the Examiner states that the specification does no provide enablement for a method of obtaining protozymes by inserting active site domains.

Claims 1, 2, 5-7, 10-14, 16 and 17 have been cancelled, and thus, the rejection is moot. Applicants respectfully submit that this rejection does not apply to newly added Claims 18-26 as they are drawn to a method of identifying enzymes with novel catalytic activity. Applicants respectfully submit that the specification fully enables a method for identifying enzymes with novel catalytic enzymes. The specification, beginning at page 15, line 17, through page 16, line31, teaches how to identify and generate high energy state rotamers capable of carrying out the desired catalytic function. Example 1 illustrates how the teachings in the specification can be applied to generate a novel

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enzyme with a desired catalytic activity. Specifically, Example 1 describes the use of one of the protein backbones described in the specification, that has the desired thermodynamic stability for the generation of a protein with novel enzymatic activity. *See e.g.*, page 9, lines 21-26 for additional protein backbones that can be used in the methods described herein. One of the computational approaches described in the specification is used to identify favorable positions for the insertion of high energy state rotamers, as well as changes to other residues in order to accommodate the substrate. See, e.g., Table 1. Finally, Example 1 describes the selection and experimental validation of proteins predicted to have the desired activity. Accordingly, Applicants respectfully submit that the specification enables a method for making proteins with novel catalytic activity and request withdrawal of the rejection of Claims 1, 2, 5-7, 10-14, 16 and 17 under 35 USC § 112, first paragraph for lack of enablement.

Rejections under 35 USC § 102

Claims 1, 2, 5-7, 13, 14, and 16 are rejected under 35 USC § 102(b) as being anticipated by WO 9853849.

WO 9853849 teaches a method of designing metalloproteins. As taught at page 4, the method comprises a number of steps, including determining a set of primary sequence mutations in the host protein which collectively form the first and second coordination spheres of a metal binding site. Notably, WO 9853849 does not teach or disclose a computational method that includes generating a set of primary sequence mutations comprising "high energy" rotamers .

In contrast, pending claims 18-26 teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein

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backbone. As described in the specification at pages 16-16, high energy state rotamers represent an energy state of a substrate. The high energy state of the substrate can include the transition state or some intermediate state on the reaction pathway of a target chemical reaction.

For an anticipation rejection under 35 U.S.C. §102 to be proper, a single reference must expressly or inherently disclose each and every element of a claim. *In re* Paulsen, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing Richardson vs. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Each of the rejected claims, as currently amended, teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone. Accordingly, WO 9853849 cannot anticipate the rejected claims and withdrawal of the rejection under 35 U.S.C. § 102 is respectfully requested.

Claims 1, 2, 5-7, 13, 14, and 16 are rejected under 35 USC § 102(b) as being anticipated by admitted prior art (see Office Action at page 7, listing Hellinga, *et al.*, Robertson, *et al.*, and Klemba, *et al.* as prior art).

As a preliminary matter, Applicants respectfully submit that they have made no admission, either in the specification or in any written communications to the Patent and Trademark Office, that Hellinga *et al.*, Roberstson, *et al.*, and Klemba, *et al.*, are "prior art". Additionally, Applicants submit that the mere listing of these three references in the specification cannot be taken as an admission that the references are prior art against the claims.

Hellinga *et al.*, Robertson *et al.*, and Klemba *et al.*, all teach methods for generating metal binding proteins. However, none of the cited references teach a teach

methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone.

As discussed above, each of the rejected claims, as currently amended, teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone. Accordingly, Hellinga *et al.*, Robertson *et al.*, and Klemba *et al.* cannot anticipate the rejected claims and withdrawal of the rejection under 35 U.S.C. § 102 is respectfully requested.

Rejections under 35 USC § 103

Claims 10-12, 16 and 17 are rejected under 35 USC § 103 (a) as obvious over WO 9853849 or Hellinga et al., or Robertson et al., or Klemba et al. in view of Brenner et al or admitted prior art (see Office Action page 7).

Applicants assume that the following 8 rejections are being applied against Claims 10-12, 16 and 17:

1) WO 9853849 in view of Brenner et al.;

2) WO 9853849 in view Hellinga, et al., Robertson et al., and Klemba et al.;

3) Hellinga et al in view of Brenner et al.;

4) Hellinga et al in view of Robertson et al. and Klemba et al.;

5) Robertson et al. in view of Brenner et al.,

6) Robertson et al. in view of Hellinga et al., and Klemba et al.;

7) Klemba et al. in view of Brenner et al.; and,

8) Klemba et al. in view of Hellinga et al., and Robertson et al.

While these rejections are argued together, Applicants retain the right to argue these rejections separately if required.

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The teachings of WO 9853849, Hellinga *et al.*, Robertson *et al.*, and Klemba *et al.* have been discussed above.

Brenner et al., teach a quantitative protein design system that can be used design proteins that fold. However, Brenner does not teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone.

When rejecting claims under 35 U.S.C. §103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re* Bell 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. Section 2142. In making a *prima facie* case, the cited references must teach or suggest each limitation of the rejected claims. *Id.* As pointed out above, WO 9853849, Hellinga *et al.*, Robertson *et al.*, and Klemba *et al.* do not teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone. This deficiency is not overcome by Brenner *et al.* Accordingly, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Claims 1,2 5-7, 13, 14 and 16 are rejected under 35 USC 103(a) as obvious over references teaching protein design methods, (e.g., U.S. Patent Nos. 6, 188,965, 6,269,312 and other references cited on lines 35 to p.3 line 2) in view of Anderson et al., U.S. Patent No. 6, 180343. See Office Action page 8.

Applicants assume that by other references cited on lines 35 to p. 3, line 2, the Examiner is referring to the following references: Dahiyat and Mayo, 1997, Science, 278: 82-87; Harbury, et al., 1998, Science, 282: 1462-1467; Street and Mayo, 1999,

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Structure Fold Des, 7:R105-109; Raha, et al., 2000, Protein Sci., 9:11-6-1119; and, Gordon, 1999, Curr Opin Struct Biol., 9:509-513. Thus, Applicants assume that the following 7 rejections are being applied against Claims 1, 2 5-7, 13, 14 and 16:

1)   U.S. Patent No. 6, 188,965 in view of Anderson et al.;

2)   U.S. Patent No. 6,269,312 in view of Anderson et al.;

3)   Dahiyat and Mayo in view of Anderson et al.;

4)   Harbury in view of Anderson et al.;

5)   Street and Mayo in view of Anderson et al.;

6)   Raha in view of Anderson et al.; and,

7)   Gordon in view of Anderson et al.

While these rejections are argued together, Applicants retain the right to argue these rejections separately if required.

As pointed out by the Examiner, U.S. Patent Nos. 6, 188,965 and 6,269,312, Dahiyat and Mayo, 1997, Science, 278: 82-87; Harbury, et al., 1998, Science, 282: 1462-1467; Street and Mayo, 1999, Structure Fold Des, 7:R105-109; Raha, et al., 2000, Protein Sci., 9:11-6-1119; and, Gordon, 1999, Curr Opin Struct Biol., 9:509-513 teach computational methods for designing proteins.

Anderson et al. teach the use of green fluorescent protein fusion constructs.

As pointed out above, each of the rejected claims, as currently amended, teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone. None of the references cited by the Examiner teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone.

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When rejecting claims under 35 U.S.C. §103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re* Bell 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. Section 2142. In making a *prima facie* case, the cited references must teach or suggest each limitation of the rejected claims. *Id.* As none of the references cited by the Examiner teach methods for identifying enzymes with novel catalytic activity by inserting one or more high energy state rotamers into a protein backbone, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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